HELLENIC REPUBLIC
National and Kapodistrian University of Athens
EST. 1837

School of Health Sciences and School of Medicine and Department of Pharmacy

Interdisciplinary Postgraduate Studies Program

M.Sc. course in Nanomedicine

Applications of Nanotechnology in Neurosurgery

Dimitrios Giakoumettis MD, MSc, PhD

Neurosurgeon

Scientific committee

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Submitted on August 2019

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To my wife and my newborn son who
stand by my side in every step I make

Table of Contents

ABBREVIATIONS

AD	Alzheimer's disease
AVM	Arteriovenous malformations
BBB	Blood-brain barrier
BMP-2	Bone morphogenetic protein-2
CAC	Critical aggregation concentration
CM	Cavernomas
CMC	Critical micelle concentration
CNS	Central nervous system
CSF	Cerebrospinal fluid
CTs	Capillary telangiectasias
DLVO	Derjaguin, Landau, Vervey, and Overbeek theory
DVA	Developmental venous anomalies
GBM	Glioblastoma multiforme
GGTase I	Geranylgeranyltransferase I
HD	Huntington's disease
HIV	Human immunodeficiency virus
HLB	Hydrophilic-lipophilic balance
HTT	Huntingtin gene
LCs	Liquid crystals
LDL	Low-density lipoprotein
MAG	Myelin-associated glycoprotein
MAOBIs	Monoamine oxidase type B inhibitors
MBP	Myelin basic protein
miRNA	Micro-RNA
MNPs	Magnetic nanoparticles
MPIOs	Magnetic iron oxide nanoparticles
MR	Magnetic resonance
NMDA	N-methyl-D-aspartate
NPs	Nanoparticles
NSET	Nanoscale Science, Engineering and Technology
PAMAM	Polyamidoamine
PD	Parkinson's disease
PEEK	Polyetheretherketone
PEG	Polyethylene glycol
PEG-PLA	Poly (ethylene glycol)- poly (lactic acid)
PLGA	Poly lactide-co-glycolide
PMLA	Poly-b-l-malic acid
QD	Quantum dots
RONS	Reactive oxygen and nitrogen species
ROS	Reactive oxygen species
SPIONs	Superparamagnetic iron oxide nanoparticles
TBI	Traumatic brain injury
tPA	Tissue plasminogen activator
USPIONs	Ultra-small superparamagnetic nanoparticles
VEGF	Vascular endothelial growth factor

ABSTRACT

Background: Any object, material or particle with one, two or three of the outer dimensions smaller than 100 nm can be defined as nano-object, nano-material, or nano-particle respectively. Nanomedicine is the application of nanotechnology to medicine and is defined by the collaboration of an interdisciplinary field of sciences. Nanoparticles are the building blocks of nanomedicine and they are organized in disperse nanosystems, which are further categorized in molecular, colloidal, and coarse dispersions.

Objective: The objective of this study is to review the current developments of nanotechnology that are of use in different sections of neurosurgery.

Methods and Materials: We conducted a systematic review according to the PRISMA statements. Inclusion and exclusion criteria were applied for any nanomedical or nanotechnological advances in terms of neurosurgery. The search was performed using the Boolean logic of the advanced search of the PubMed database and by scanning reference lists of the resulting articles.

Results: The search yielded 1984 items and full texts of 190 articles were retrieved for further investigation. A total of 78 original studies were included in our review. Most of the studies, a total of 43, were about neuro-nanotherapy, while a total of 47 were about neuro-oncology.

Conclusion: The brain is probably the most challenging target organ, with the main obstacle to overcome the blood-brain barrier (BBB). Incidence of brain pathology is rising as the population ages, and convectional medications prove to be insufficient for dealing with many neurological diseases. Nanotechnological research is still young, yet quite promising and many new nanosystems are nowadays under development against brain pathology.

INTRODUCTION

The definition of Nanotechnology is given by the "Interagency Subcommittee on Nanoscale Science, Engineering and Technology (NSET)" of the US Federal Office of Science and Technology Policy. According to NSET, nanotechnology is defined as "The research and technology development at the atomic, molecular or macromolecular levels, devices and systems of their small and/or intermediate size. The novel and differentiating properties and functions are developed at a critical length scale of matter typically under 100 nm". Any object, material or particle can be nano-defined respectively, only if one, two or three of the outer dimensions are smaller than 100 nm. Nanomedicine is the application of nanotechnology to medicine and is defined by the collaboration of an interdisciplinary field of sciences for diagnosing, treating, curing, monitoring, predicting and preventing diseases (1, 2).

The first scientific report of nanotechnology (without the use of the term "nanotechnology") was made during the speech of Richard Feynman entitled: "There's plenty of room at the bottom" during the American Physical Society dinner in 1959. The term nanotechnology was first introduced by Professor Norio Taniguchi from the University of Sciences in Tokyo, in 1974, in his thesis entitled: "On the basic concept of Nanotechnology", where he precisely described the formation of materials with dimensions of a nanometer. During the 1980s, the term reappeared and was redefined by Eric Drexler, the President of Foresight Institute in his book "Engines of Creation: The Coming Era of Nanotechnology" published in 1986, in an effort to popularize the term.

Pharmaceutical nanotechnology provides new techniques for designing and developing medicinal products, by enhancing the properties of both new molecular entities and well-known drugs. Nanoparticles (NPs) are the basic components of pharmaceutical nanotechnology and they are used to develop non-biological complex drugs. There is a diversity of nanoparticle platforms (nanosystem) such as liposomes, polymer conjugates, metallic nanoparticles, polymeric micelles and dendrimers. The design and production of a nanosystem (or nanocarrier) demand the perfect comprehension of the structure and function of the biological cells, and their mechanisms of preservation and survival. It is well known that the most valuable part of a biological

system is the cell membrane. It is a natural liquid crystal, where its structure is a double layer lipid with phospholipids as dominant components. Nanoparticles that are used in drug delivery systems are generally <100 nm in at least one dimension and consist of different biodegradable materials. The latter can be natural or synthetic polymers, lipids, or metals and are taken up by cells more efficiently than larger micromolecules (3).

In chemistry, a colloid is a mixture in which one substance of microscopically dispersed insoluble particles is suspended throughout another substance. In colloidal dispersions, dispersion phase particles present a hydrodynamic diameter between 1 and 500 nm. The pharmaceutical industry tries to develop high-quality colloidal biomaterials, emphasizing in controlling their properties so when they are found in the appropriate environment, they will orient towards the desired direction. Due to the fact that the size of the dispersed phase may be challenging to measure, and colloids appear as solutions, colloids are sometimes identified and characterised by their physicochemical and transport properties. Based on the nature of the interaction between the dispersed phase and the dispersion medium, colloids can be classified as hydrophilic colloids, where the colloid particles are attracted toward water while hydrophobic colloids are repelled by water. The main type of forces that appear among particles and nanocolloidal system interactions can be either attractive such as Van der Walls interactions and electromagnetic forces, or repulsive such as electrostatic, Born and Steric forces.

The objective of this study is to review the current developments of nanotechnology that are of use in different sections of neurosurgery. The main types of nanosystems will be presented as well as their physicochemical properties. Furthermore, the challenges and futures perspectives of nanotechnology in the field of neurosurgery will be discussed. Finally, this review will highlight the importance of understanding nanotechnological biological systems and their interaction with neurosurgery.

BACKGROUND

The achievements of sciences in physics, biology, chemistry but also the evolution in technology and the progress in the science of materials have helped to understand nanotechnology. Nanoparticles are classified depending on their material (Fig. 1) and can be administered in patients via a variety of routes, such as intravenous, oral, transdermal, nasal, rectal route of administration. Disperse systems can be classified according to particle size in molecular, colloidal, and coarse dispersions. In colloidal dispersions, dispersion phase particles are in sizes between 1 and 500 nm, in coarse dispersions exceed

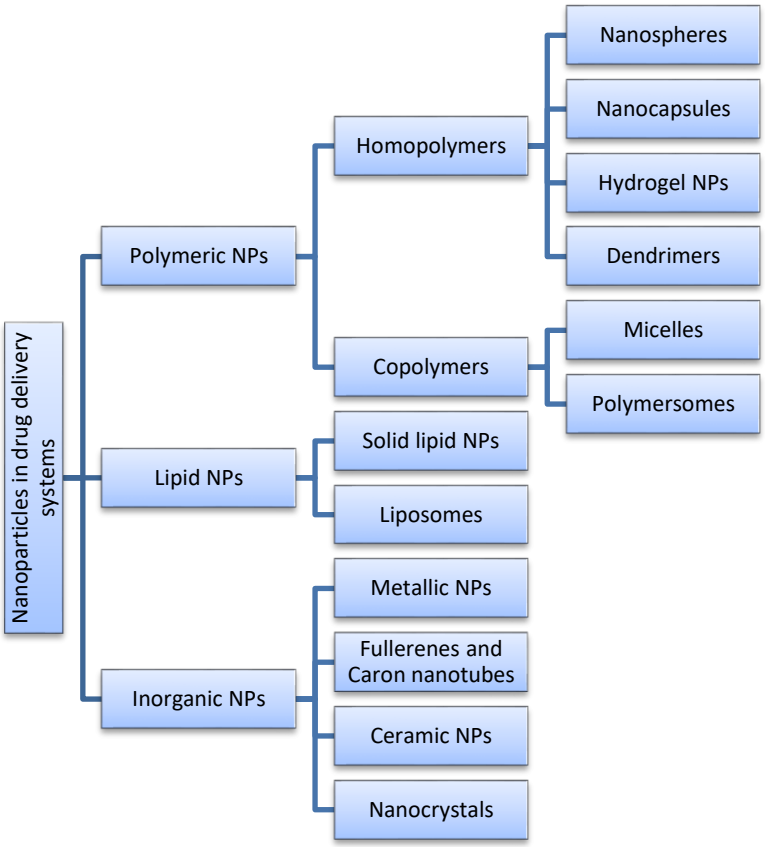

Figure 1. Classification of Nanoparticles (NPs) depending on their material.

500 nm, and in molecular are less than 1 nm size (4). It must be highlighted that colloidal are considered the systems in which the dispersed particles are in sizes between a few nanometers to a few thousand nanometers. Even though dispersed particles of a few nanometers may look like they act as molecular solutions, they exhibit completely different properties when compared to that of the same concentration solution of particles in molecular size.

Stability of a nanosystem

The random motion of particles suspended in a fluid (liquid or gas) resulting from their collision with the fast-moving molecules in the fluid is called Brownian motion. The upper limit of the particle's size is the point where Brownian motion allows and reserves the particle in dispersion state. The attractive interactions between the particles are minimum and proportional to their masses. Therefore, a colloidal system rests in an equilibrium state between Brownian motion and interaction forces between particles. The dispersed particles of the colloidal systems have high surface per volume unit. Therefore, the interface effects can be interpreted according to the surface tension and the ζ-potential (5). Due to the high surface per volume unit, the system has great surface energy that is expressed from the following equation:

$$E = \gamma S$$

where γ is the surface tension, the force opposing the surface growth due to the attraction of water molecules or interactions of dispersed particles to the inner fluid, and S is the particles' surface. Z-potential is an important physical parameter which corresponds to the total charge of nanoparticles' slipping plane but not the surface charge. It can offer information pertaining to the interaction of nanoparticles between them or with cells and information on the nanosystem's stability. The latter has been described by the Derjaguin, Landau, Vervey, and Overbeek (DLVO) theory, which represents a dispersion stabilizing model of calculating the interactions in aqueous colloidal suspensions and the respective aggregation rates (6). The theory uses ζ-potential to explain that as two particles approach one another their ionic atmospheres begin to overlap, and repulsion force is developed. In other words, it assumes that the interaction forces can be well approximated by a superposition of van der Waals and double-layer forces. In a symmetric system or the case of homoaggregation, van der Waals forces are attractive and double layer forces repulsive. When one deals with asymmetric systems and heteroaggregation, the situation can be more complex. While, van der Waals forces are generally attractive, the double layer forces can be attractive, repulsive, or both. Moreover, the effects of charge regulation can become important. DLVO theory is further capable of describing experimental situations relatively well. In some cases, this theory can describe interaction forces as well as

aggregation rate constants quantitatively. Deviations may persist, however, especially at higher salt levels (7). Van der Waals force interaction energy between particles with different shapes can be approximated by the method Derjaguin approximation and thus calculated as the energy between: i) two spheres,

$$W(D) = -\frac{A}{6D}\frac{R1R2}{(R1+R2)}$$

ii) sphere and surface,

$$W(D) = -\frac{AR}{6D}$$

iii) two surfaces

$$W(D) = -\frac{A}{12\pi D^2}, per\ unit\ area$$

Where W(D) is the interaction energy between the combinations, A is the Hamaker constant, R is the curvature radius of the sphere, and D is the perpendicular with the surface axis that passes at the point where the molecule is. The theory is summarised in Fig. 2.

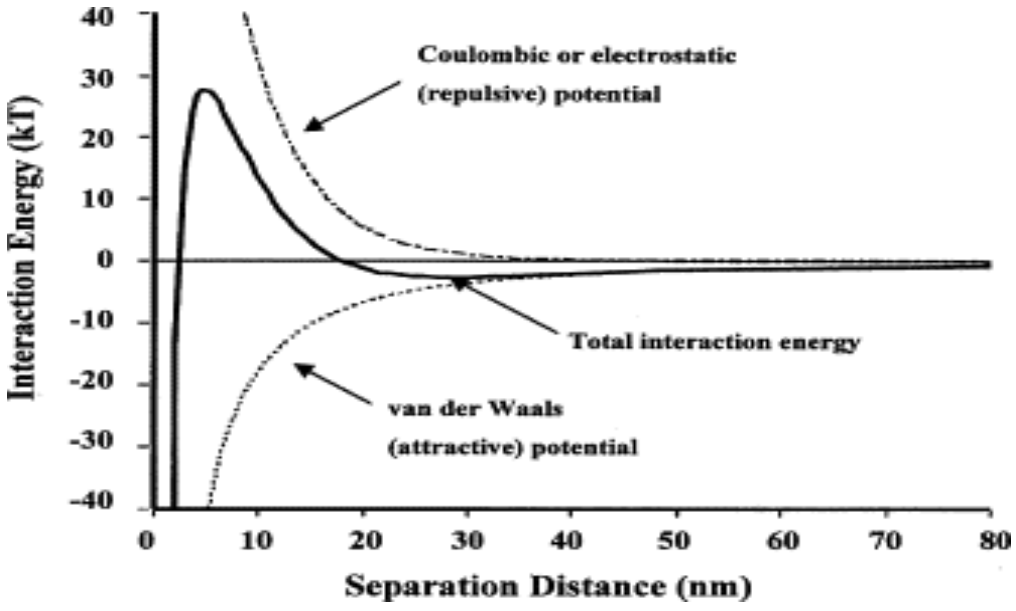

Figure 2. Schematic representation of DLVO stability theory as net energy after the combination of the van der Waals and double layer forces. (Adapted from: Adair JH, Suvaci E, Sindel J. Surface and Colloid Chemistry. In: Buschow KHJ, Cahn RW, Flemings MC, Ilschner B, Kramer EJ, Mahajan S, et al., editors. Encyclopedia of Materials: Science and Technology. Oxford: Elsevier; 2001. p. 1-10).

Surface Plasmon Resonance

The basis for measuring adsorption of a material onto the planar metal (usually gold or silver) surfaces or onto the surface of metal nanoparticles is localized surface plasmon resonance (LSPR). The latter is a nanoscale effect that causes metal nanoparticles to absorb and scatter electromagnetic radiation of wavelengths larger than the particles themselves. More specifically, the oscillating electric field of an electromagnetic wave (i.e. light) can induce coherently oscillation of the conduction electrons of metal nanoparticles. The collective excitations of conductions electrons in metals are called “plasmons”. The electromagnetic surface wave that propagates in a direction parallel to negative permittivity/dielectric material surface is called “surface plasmon polariton”. The wave is on the boundary of the conductor and the external medium (e.g. air, water), and therefore the oscillations are very sensitive to any change of this boundary. In order to excite surface plasmons in a resonant manner an electron bombardment or incident light beam can be used. The incoming beam must match its momentum to that of the plasmon. LSPR condition is defined by several factors, including the electron-properties of the nanoparticle, the size and shape of the particle, temperature and the dielectric environment. Electronic and magnetic surface plasmons obey the following dispersion relation:

$$K(\omega) = \frac{\omega}{c}\sqrt{\frac{\varepsilon_1\varepsilon_2\mu_1\mu_2}{\varepsilon_1\mu_1 + \varepsilon_2\mu_2}}$$

Where ε is the relative permittivity, μ is the relative permeability of the material, ω is the angular frequency and c is the speed of light in a vacuum. When the surface plasmon wave interacts with a local particle or irregularity, e.g. rough surface, part of the energy can be re-emitted as light. This emitted light can be detected behind a metal film from various directions. For NPs, localised surface plasmon oscillations can give rise to the intense colours of suspensions or sols containing the NPs.

Self-assembly

Self-assembly is a spontaneous process of organisation of chaotic molecular units into ordered structures as a result of intramolecular and intermolecular interactions. The

process of assembly is controlled by the balance of attractive and repulsive forces within and between molecules. The most straightforward and extensively known self-assembled structure in a biological system is the lipid membrane structure. The cell membrane consists of lipid bilayers that are arranged in such a way that their hydrocarbon tails face one another to make a hydrophobic bilayer while their hydrophilic head groups are exposed to aqueous solutions on each side of the membrane (8).

Amphiphilicity is one of the main driving forces for self-assembly of surfactants. The thermodynamic properties of amphiphiles in solution are controlled by the strong tendency of hydrophobic tails to avoid direct contact with water (9). Therefore, micelle formation is dictated by two opposite forces, the attractive force between the insoluble blocks, which leads to aggregation, and the repulsive one between the soluble blocks preventing unlimited growth of the micelle. These forces can be depletion attraction, capillary forces, dipole-dipole attractions, or some combination of the above. At the same time, the interaction of the soluble blocks and the solvent is responsible for the stabilisation of the micelles. Surfactants are classified based on the charge of the hydrophilic group and they can be either ionic (anionic or cationic) or non-ionic. Self-assembly of amphiphiles is of fundamental importance in diverse fields of application including pharmaceutical, food and cosmetic formulations.

Liquid crystals

Liquid crystals (LCs) are a state of matter which has properties between those of conventional liquids and those of solid crystals. LCs that their transition state depends on the temperature are called thermotropic, whilst when the transition state depends both on the temperature and their concentration in the medium that they are found, are called lyotropic. The fundamental difference between the thermotropic and lyotropic LCs is that the anisotropic dispersion forces between structural units are responsible for the thermotropic transitions, whereas the dispersion media is primarily responsible for the lyotropic transition of the LCs.

Thermotropic LCs are divided into enantiotropic and monotropic LCs. Enantiotropic transit to liquid crystalline state either by lowering the temperature of a liquid or by raising the temperature of a solid. Monotropic transit into the liquid crystalline state either by

lowering the temperature of a liquid or by raising the temperature of a solid, but not simultaneously. If the temperature is too high, the rise in energy and therefore in the motion of the components will induce a phase transition and consequently the LC will become an isotropic liquid. On the contrary, if the temperature is too low to support a thermotropic phase, the LC will change to the gel phase. The thermotropic LCs are categorised depending on their molecular structure as nematic, smectic, and columnar. In nematic LCs, the molecules are free to move to all directions, are parallel without a pattern, and move along the direction axis. In smectic LCs, the molecules present a transition grade, set up along one direction, and tend to line up in layers or plateaus. Last but not least, in columnar LCs, the molecules are in disk shape forming piles (Fig.3).

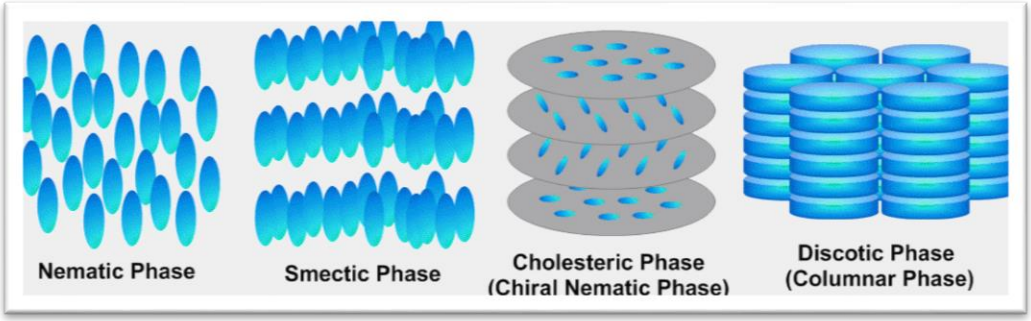

Figure 3. The subphases of thermotropic LCs. (Source: https://www.tcichemicals.com/data/contents/category_index_preview/en/st7520000002sww1-img/48.gif)

The lyotropic LCs consist of one polar and one non-polar part. The polar part is an ionised chemical group, while the nonpolar is a hydrocarbon chain which can be saturated or unsaturated. The lyotropic LCs are found on the surface of the particle due to their chemical properties and they are called this way because they are a mixture of two or more, different to each other, components, not being in liquid crystalline phase on their own. The lyotropic LCs are divided into two categories. The first one is the solutions of anisotropic colloidal macromolecules or particles whose structure presents robust orientation such as polymer bars with low rigidness. The second one is the non-liquid crystalline molecules in solutions that are self-assembled in supramolecular structures that are self-organised in LCs. The lyotropic systems aggregation occurs only when the concentration of the amphiphile exceeds a critical concentration, known variously as the critical micelle concentration (CMC) or the critical aggregation concentration (CAC),

whereas the phenomenon of self-assembly is dependent only on the concentration of the amphiphile.

As far as it concerns the membrane of biological cells, its structure is a lipid double layer with phospholipids as dominant components. In both sides of the double layer and on the inside, there are proteins and other biomolecules. The phospholipids are amphiphilic molecules that are composed of polar head groups and two hydrocarbon chains. The length of the lipid chain and their relative flexibility control the temperature limits of the membrane crystalline state. In lower temperatures, the membrane transits from the liquid crystalline phase to the gel phase. It has been observed that the transition temperature from the liquid crystalline phase to the gel phase of the cells in the living organisms is slightly higher than that of cell membrane phospholipids.

The lyotropic liquid crystal nanostructures are the dominant structures in living organisms and their role in the cell function and preservation of life is definitive. The contribution of the lyotropic structures in the organisation and fluidity of the cell membrane as well as in the preservation of homeostasis is characterised as definitive for the evolution process of the living organisms. Furthermore, the lyotropic LCs have a special interest in the field of biomimetic chemistry. These membranes that are in the liquid crystalline state have on their inside macromolecules, like protein receptors and other surface macromolecules that participate in the organisation according to the absolute cooperativity with the main structural elements of the membrane. The phenomenon of conformational polymorphism plays a vital role as it affects the physical properties of phospholipid transition phases. As a result, the release and the pharmacokinetic profile of the bioactive molecule that is encapsulated into the nanosystem are changed, as long as phospholipids are the structural units of such nanosystem.

As already mentioned, understanding the biological properties of the cells is very important in order to produce a nanosystem. The cell membrane has an LC behavior, so it is necessary to present their properties. The most characteristic property of LCs is their behavior inside an electric field, which depends on the molecular charge of the LC. The LC molecule has two charged molecules, one positive and one negative. When an electric field is applied to them, the charged sides try to resist the forces and are set along the electric

field direction. However, if the LC does not respond to the electric field, charged sides exchange their positions and form a dipole (Fig. 4).

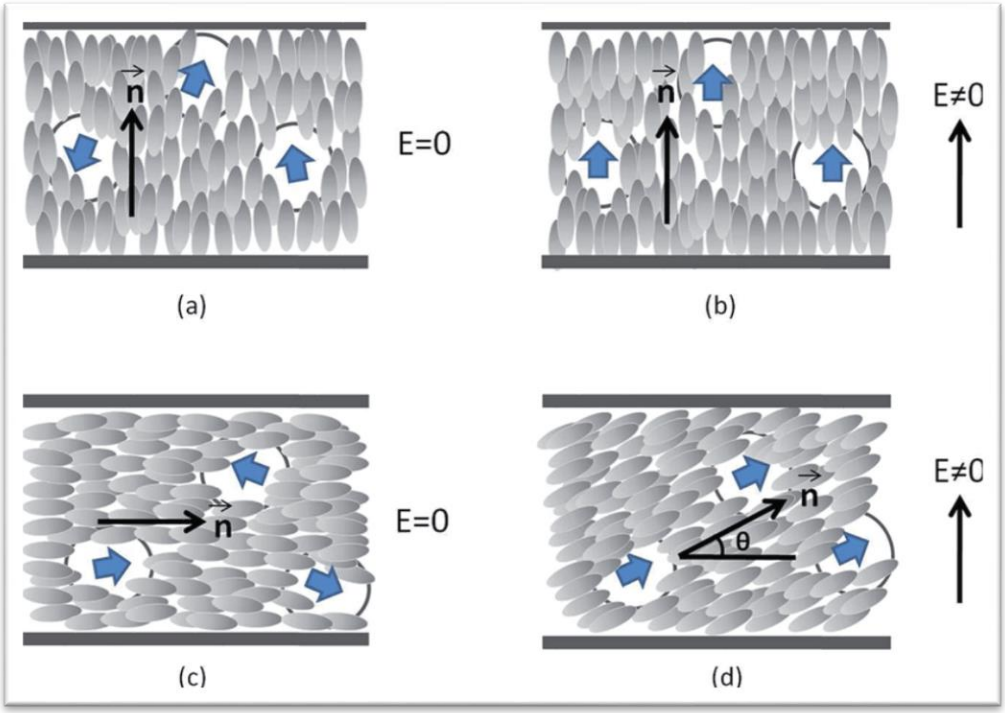

Figure 4. A schematic illustration of the liquid crystal molecular orientation in the nematic phase: a doped liquid crystal with homeotropic orientation in a capacitive cell (a) without and (b) with an electric field. Most of the liquid crystal molecules correspond with the field by arranging their longitudinal axis across the electric field. Planar orientation of a doped liquid crystal (c) without and (d) with an electric field. Thich arrows represent the dipole of the ferroelectric field. (Adapted from: Lin Y, Daoudi A, Dubois F, Blach J-f, Henninot J-F, Kurochkin O, et al. A comparative study of nematic liquid crystals doped with harvested and non-harvested ferroelectric nanoparticles: Phase transitions and dielectric properties. RSC Adv. 2017;7:35438-44).

In addition, another important property of LCs is their reaction in magnetic fields. When a magnetic field is applied, the dipoles are oriented like North and South Pole along the direction of the magnetic field, giving that way to the LC's molecules a vertical or a parallel direction to the magnetic field.

Main types of Nanosystems

Drug delivery nanosystems are used to modify the solubility, body distribution, biocompatibility, targeting, toxicity and drug release of an active compound. The last decades numerous types of nanosystems for drug delivery have been developed, but only a few of them have managed to present satisfying results in clinical studies and become

commercially available. In order to comprehend the phenomena analysed above, it is essential to determine the building blocks of each nanosystem and the factors that led to the development of each one of them (10). The main types of nanosystems are described briefly, and afterwards the most important and widely used will be analysed thoroughly (Table 1).

Drug delivery systems	Building blocks (components)	Main applications
Liposomes	Phospholipids, cholesterol	Delivery of anticancer drugs
Niosomes	Non-ionic surfactants	Drug delivery
Dendrimers	Polymers	Drug delivery, Sensors, Nanoelectronics etc
Micelles	Amphiphilic molecules	Drug delivery, Imaging
Polymersomes	Polymers	Delivery of biomolecules
Metal Nanoparticles	Metals (e.g. Au)	Bio-Imaging, Theranostics
Quantum Dots	Metal ions, Colloid stabilisers	Biological sensing, Cellular labelling, Photodynamic therapy etc
Nanogels	Hydrophilic or amphiphilic polymer chains	Drug delivery
Carbon Nanotubes	Carbon	Few (due to toxicity)
Silica Nanoparticles	SiO2	Biomedical Imaging, Drug delivery
Magnetic Nanoparticles	Magnetic materials (e.g. Fe, Ni)	Biomedicine, Catalysis, Sensors, MRI, Theranostics

Table 1. Main types of Nanosystems for drug delivery.

Liposomes

Liposomes are spherical entities with an aqueous interior enclosed by bilayers of phospholipids. They constitute a very promising type of nanocarrier and have been widely used in the last decades mainly for the targeted delivery of anticancer drugs, due to the plethora of advantages they present (11). They are composed of phospholipids which in aqueous media can self-assembly to form spherical vesicles. Cholesterol is often added to enhance the stability of liposomes. In addition, polymers can alter the properties of those systems either by incorporation in the lipidic bilayers or by modifying the surface of the system. These systems are known as stealth or chimeric liposomes. According to the percentage (molar ratio) of its ingredients, the properties and the colloidal behavior of the liposome can be controlled, in order to produce functional systems and efficient drug delivery.

Furthermore, the extensive use of liposomes derives from the large number of advantages that they present over conventional systems. Among these, high biocompatibility, biodegradability, low toxicity, protection and targeted delivery of the active substance, prolonged half-life in blood circulation and satisfying solubility in aqueous media and, therefore, in biological fluids, are the most important ones. Their ability to deliver both water-soluble and lipid-soluble drugs makes them ideal carriers for almost every type of drug. Liposomes can

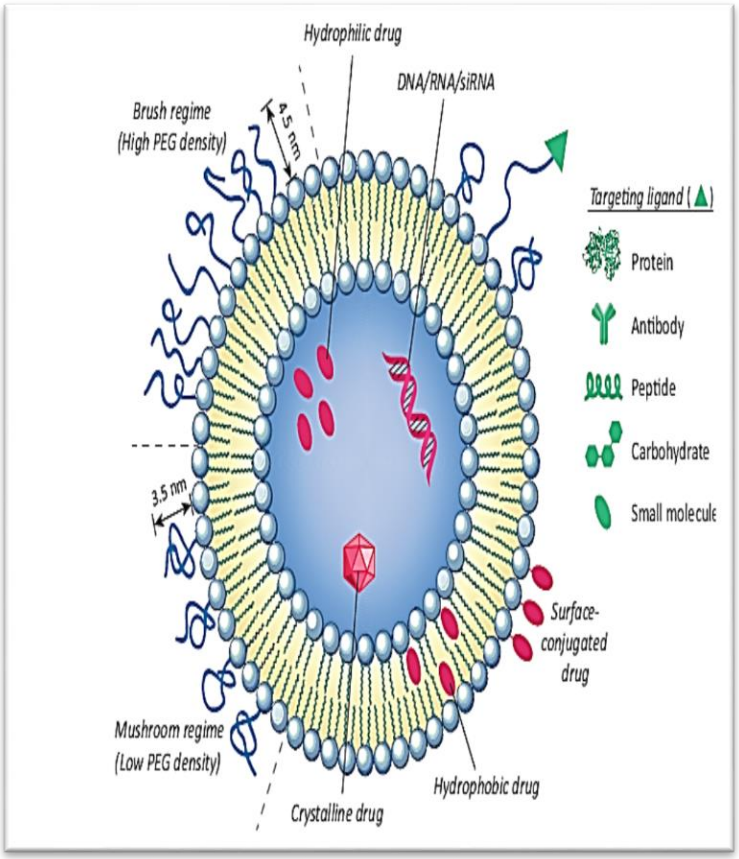

Figure 5. Liposomal structure composed of different in nature drugs and macromolecules incorporated into different domains of the liposomal structure that can deliver them to the target tissues. (Source: https://www.intechopen.com/media/chapter/46983/media/image1.png)

also present low immunogenicity by modifying their surface (e.g. by adding PEG) and therefore enabling them to avoid opsonisation. (Fig. 5)

Liposomes have been used as carriers of drugs, cosmetics, nutraceuticals and vaccines, but until now, their most important application is the targeted delivery of anticancer agents (e.g. doxorubicin).

Niosomes

Niosomes are nanocarriers composed mainly by non-ionic surfactants, aqueous media and bilayer membrane additives (e.g. cholesterol) that self-assembly in aqueous media to form a spherical vesicle (Fig. 6). Non-ionic surfactants are amphiphilic agents that consist of a hydrophilic head and a hydrophobic tail and have zero charges (e.g. Spans, Tweens, Polysorbates etc) (12). They were developed in order to find an alternative system to liposomes, as the last one presents several difficulties related to their production and their in vivo behavior. Therefore, niosomes present better physicochemical stability and they can easily be produced on a large scale. Also, one of the main reasons that led to the development of niosomes is that they are more cost-effective than liposomes, as lipids are more expensive than surfactants (13).

Their behavior, self-assembly and applications are very similar to liposomes. Their surface can also be modified in order to ameliorate the functionality of the system, and they present low toxicity and high biodegradability. According to the HLB (Hydrophilic-Lipophilic Balance), cholesterol can be added in order to enhance the stability of the surfactant bilayer. Overall, the main obstacle that niosomes have managed to overcome compared to liposomes is physical stability problems, chemical degradation and oxidation and this makes them a very promising nanosystem (14).

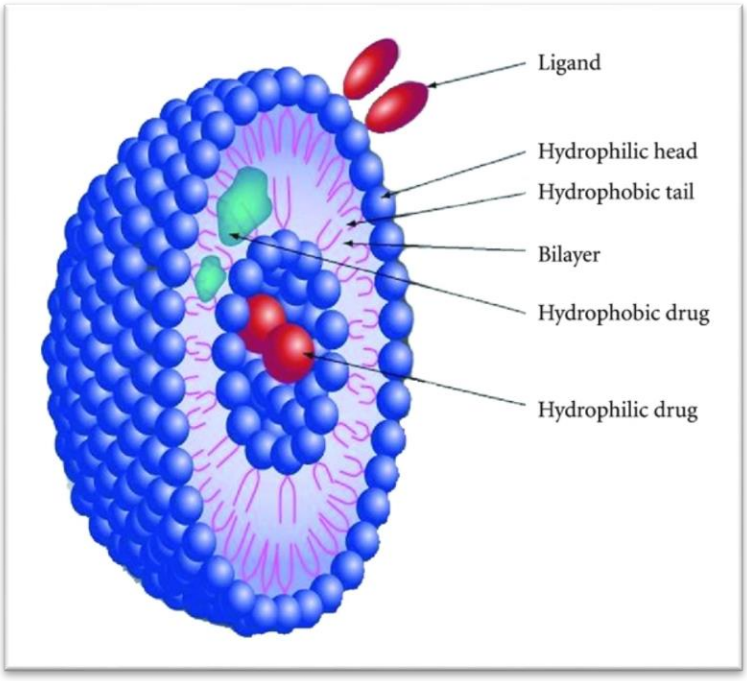

Figure 6. Structure of a non-ionic surfactant vesicle (niosome, Nonionic surfactant vesicular systems for effective drug delivery). (Adapted from: Christoforidis J, Chang S, Jiang A, Wang J, Cebulla C. Intravitreal Devices for the Treatment of Vitreous Inflammation. Mediators of inflammation. 2012;2012:126463).

Dendrimers

Dendrimers are a particular type of synthetic polymers that can contribute as vectors, in the development of more enhanced anticancer therapies. These highly symmetrical and branched polymers have attracted much attention in recent years due to their specific physical and chemical properties arising from their organised construction. As far as it concerns the dendrimers structure, they are polymeric molecules (e.g. Polyamidoamine dendrimers Fig. 7, left), chemically synthesised with well-defined shape and almost spherical shape tree with diameters usually between 2 and 10 nm. These structures offer great advantages, as their extremely precise and controlled architecture provides a predictable molecular weight, an increase of drug stability, biodegradability and biocompatibility (15).

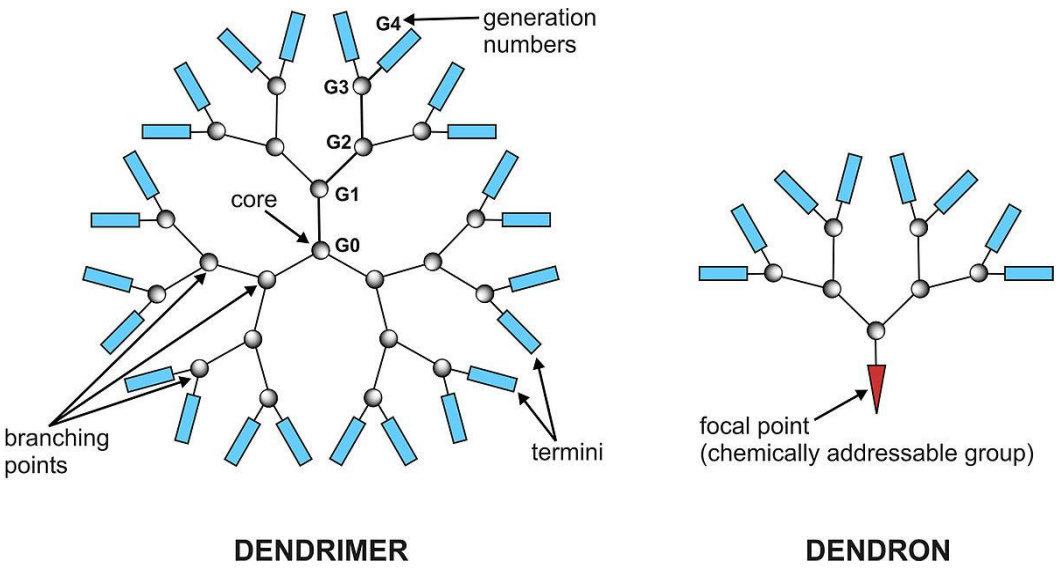

Figure 7. General structure of a dendrimer (Left). 2nd generation dendrimer Polyamidoamine (PAMAM) (Right). (Source: https://upload.wikimedia.org/wikipedia/commons/e/e8/Graphs.jpg Copyright: CC BY-SA).

Dendrimers can be divided into three parts: center, branches and surface area. The core determines the shape, size, direction and municipality of dendrimers. The middle part is formed by the branching units and the functional groups of the terminals are placed at the periphery of this structure (Fig. 7, right). Dendrimers are developed from a central core, with each subsequent step representing a new generation. Increasing generations bring on larger molecular diameters. The surface groups may function as gates that control the entry and exit of guest molecules from the interior of the dendrimer. These properties also enable better control and biodistribution of the drug in the body (16).

Micelles

Micelles are formed by the spontaneous self-assembly of amphiphilic molecules in aqueous media. Namely, they are spherical vesicles whose core is formed by the hydrophobic tails and the hydrophilic/polar part forms the surface of the micelle (Fig. 8). Corresponding to liposomes, they can deliver both hydrophilic

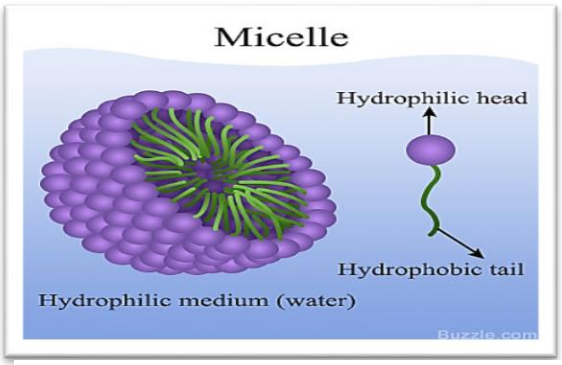

Figure 8. General Structure of a Micelle. Source: (http://www.buzzle.com/images/diagrams/micelle.jpg)

and lipophilic agents, and they present similar advantages to liposomes. Their main applications concern targeted drug delivery to tumors and imaging.

Two types of micelles are widely used and present numerous advantages as drug delivery systems: the polymeric and the mixed micelles. Polymeric micelles are composed of block copolymers (mix of hydrophilic and hydrophobic chains) where in aqueous media the core is formed by the hydrophobic chains and the hydrophilic parts surround the core by forming a hydrated shell. Micellar carriers present advantages such as high drug loading capacity, extended circulation time, controlled release of the drug, targetability etc. Mixed micelles are a combination of amphiphilic systems (e.g. surfactants, polymers, copolymers) with different properties than an amphiphile alone, and are used mainly for the delivery of hydrophobic drugs.

Polymersomes

Block copolymers are structures composed of different polymers. They have the ability to self-assembly in aqueous media and form complex membranes which present high stability. These membranes form “pseudo-spherical” systems called polymersomes. They are considered to be biomimetic membranes and can be used as vesicles for the delivery of biomolecules and biological agents such as membrane proteins (17).

The formation of the membrane is favored when multiblock copolymers are used (e.g. Fig. 9 ABABA copolymers) as long as the hydrophobic/hydrophilic proportion permits the self-assembly towards a polymersome. They present the ability to avoid the immune system by making them stealth (e.g. by adding a considerable amount of PEG), they can transfer drugs of high molecular weight and, most importantly, they are unique because they can deliver a wide range of biomolecules and bioactive molecules and they offer the possibility to control the release rate of the drug (18, 19).

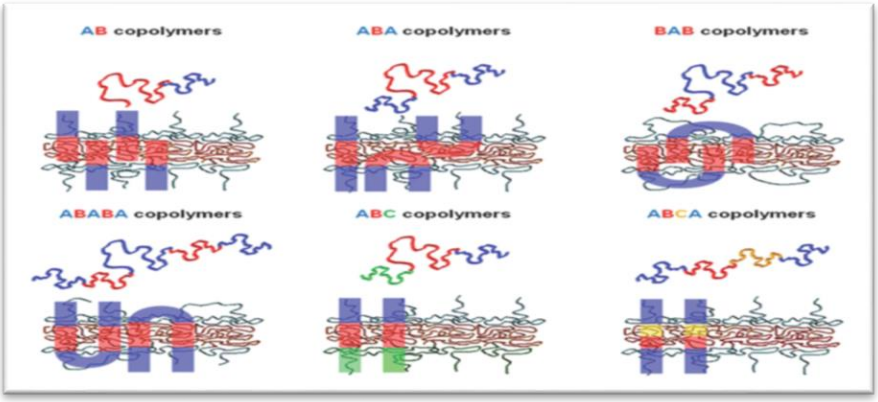

Figure 9. Membrane conformation of polymersomes formed by diblock, triblock and multiblock copolymers. A: hydrophilic, B: Hydrophobic. (Adapted from: "Pharmaceutical Nanotechnology Fundamentals and Practical Applications", by Costas Demetzos, ISBN 978-981-10-0791-0 (eBook), DOI 10.1007/978-981-10-0791-0).

Quantum dots

Quantum dots (QD) are colloidal semiconductor nanocrystals composed of a metalloid crystalline core (such as cadmium selenium) shielded by an intermediate unreactive metallic shell (such as zinc sulfide) (20). They are designed with a few hundred atoms, usually consisting of II-VI or III-V group type atoms of the periodic system. These nanocrystals have dimensions smaller than the Bohr's radius. For nanoparticles made from semiconducting material the energy is quantised like in atoms (Energy Quantization = Energy Takes Only Discrete Values in Atoms and Nanoparticles).

Such an inorganic nanoparticle exhibits high brightness, long-term photostability and size-tunable narrow emission spectra. These characteristics can turn it into a diagnostic imaging technology (21). Due to their high surface area, their potential of being co-incorporated with a variety of diagnostic and therapeutic molecules, and their ability to act as a carrier vehicle for blood-to-brain drug delivery, constitute quantum dots a very promising targeted therapy for central nervous system (CNS) disorders.

The outer coating of quantum dots can be chemically functionalized with bioactive molecules. The latter promotes: i) aqueous solubility and desired bioactivity, ii) targeting of specific molecules, and iii) carrying therapeutic molecules (22). It has been found that Captopril-conjugated CdSe/ZnS-core/shell-typed quantum dots (QDs-cap) when administered intraperitoneally in mice, they were delivered through systemic blood

circulation into the liver, the spleen, the kidney as well as the brain, which showed the possibility of such quantum dots to penetrate the blood-brain barrier (BBB) (23). It is widely known that the Tf receptor is a specific BBB transporter that allows only selected molecules to move across the BBB; for that reason, lysine coated CdSe/CdS/ZnS quantum dots have been synthesised and conjugated with Tf. It has also been reported that their migration rate in in vitro BBB model was concentration- and time-dependent after systemic administration, and therefore demonstrating a receptor-mediated transport mechanism (24). Furthermore, a cell membrane translocation peptide, TAT, has been successfully used to internalise NPs (25). Researchers have shown that TAT-conjugated CdS:Mn/ZnS quantum dots can label the brain parenchyma within a few minutes after being intra-arterially delivered to a rat brain; TAT-conjugated QDs and not QDs without TAT reached the brain tissue through endothelium without manipulating the BBB (26, 27).

Metallic Nanoparticles

Metallic nanoparticles comprise inorganic metallic or metallic oxide cores that are covered by shells. Magnetic nanoparticles (MNPs) are a type of metallic nanoparticles that consist of magnetic iron oxide nanoparticles (MPIOs) and are further subcategorised according to their hydrodynamic size to superparamagnetic (SPIONs) and ultra-small superparamagnetic NPs (USPIONs) (28). Magnetic nanoparticles are used often in MR CNS imaging because of their ability to cross over BBB. Many studies have been designed using SPIONs and USPIONs conjugated with several means of contrast, because they offer longer circulating life and better specificity (29, 30). Nevertheless, the most famous nanoparticle of this category are the gold nanoparticles. They have been extensively investigated and due to their extraordinary physico-chemical features along with a low toxicity profile they have been used in imaging, therapy and theranostics. For that reason, research has been devoted to producing a diversity of gold nanoformulations with precise and controlled sizes as well as with different morphologies. To date there are ten different forms of gold nanoparticles that have been developed and used for researched purposes: i) gold nanospheres (31), ii) gold nanoclusters (32), iii) one-dimensional gold nanorods (33), iv) two-dimensional gold nanoplates (34, 35), v) gold nanoshells (36-38), vi) platonic gold nanoparticles (39, 40), vii) hollow gold nanospheres (41-43), viii) gold nanocages,

nanoboxes and nanoframes (44-46), ix) branched gold NPs (47-49) and x) dendritic gold NPs (50-53).

Other Inorganic Nanomaterials

Nanotechnology is a rapidly evolving research area and has developed a diversity of materials in service of researchers in the last years. Carbon nanotubes come in a single or multiple-wall tube of graphic carbon. They are biocompatible, they can be easily modified, and they have a high aspect ratio (54). Their versatility is one of their outstanding traits and constitutes them as an excellent material for theranostics (55). Therefore, they can be used either for high-resolution imaging, due to their ability to absorb near-infrared light, or for therapeutic purposes because of heat production after the light absorption, that can lead to a therapeutic destructive effect on tumors (56). However, their physico-chemical characteristics, such as size, shape, charge to density ratio can present with a toxic effect on the organism (57). Even though there is ongoing research for carbon nanotubes, carbon-based materials have not convinced the research community about their safety (58).

Nanomaterial	Advantages	Disadvantages
Micelles	• Good carriers for drugs with poor aqueous solubility • Due to hydrophilic cell, there is some immune mechanism contributing to more prolonged circulation	• May dissociate before target • May not dissociate well – poor drug release
Dendrimers	• High versatility for surface functionalization • Encapsulation of drugs and nucleic acids	• Cationic surface groups may interact with membranes and proteins, resulting in cell toxicity
Hydrogels	• Controlled, stimulus responsive drug release • Scaffold for neural tissue due to good mechanical strength	• Potential reactivity due to non-cross-linked small molecules after synthesis
Nanopolymers	• Wide variety of materials and functions • Can be biodegradable	• Modifications can alter toxicity profiles
Liposomes	• Biocompatible • Biodegradable • Carry both hydrophilic and lipophilic drugs	• Low solubility and short half-life • Might undergo oxidation and hydrolysis reactions • Leakage of drug molecules

Solid lipid NPs	• Targeted drug release and good physical stability	• Low loading capacity • Drug expulsion after polymeric transition during storage
Quantum dots	• Tunable emission peaks • Long fluorescence half-life	• Limited data from in vivo studies on clinical applicability and toxicity
Magnetic NPs	• Paramagnetic properties	• Potential toxicity and sequestration within the body
Carbon nanotubes and graphene	• Scaffolds for neuroregeneration due to electrical conductivity • Biocompatibility	• Conflicting studies on cytotoxicity and genotoxicity
Gold NPs	• Photothermal agents • Radiosensitising agents	• Not clearly defined biodistribution, pharmacokinetics and toxicity

Table 2. Summary of advantages and disadvantages of the most common used nanomaterials in neurosurgery.

METHODS AND MATERIALS

The current review was conducted according to the PRISMA statement criteria (15). The literature search was from January 1, 2009 to August 3, 2019. No other temporal limits were applied. The search was open to both in vitro and in vivo studies. Inclusion criteria included nanomedical or nanotechnological advances in terms of neurosurgery. The review included only original papers published in Pubmed-indexed peer-review journals, clearly stating nanomedicine and nanotechnology in neurosurgery, the experimental model/s, and the radiological technique/s that were applied. Exclusion criteria included: papers not describing original research (i.e. reviews, perspectives, letters to the editor, commentaries, and abstracts), papers in languages other than English, description of new chemical or physical properties of nanomedical molecules or nanotechnological systems without application of biological models or without application to a neurosurgical field, and papers focusing on nanotechnology but not primarily on neurosurgery.

The search was performed using the Boolean logic of the advanced search of the PubMed database and by scanning reference lists of the resulting articles. The search terms were (((((((nanomedicine) OR nanotechnology) OR liposome) OR dendrimer) OR quantum) OR gold) OR niosome) AND neurosurgery. Eligibility assessment was performed independently in an unblinded standardised manner by two reviewers. Disagreements between reviewers were resolved by consensus. The following data were extracted from each paper: title, authors, article type, PMID, DOI, year of publication, in vitro/in vivo model, nanomedical/nanotechnological material, nano-field, neurosurgical field, the application of the system and main conclusions of the study. Unfortunately, a quantitative comparison between studies or groups was not possible because of the heterogeneity of the biological models and technical discrepancies between different nanomedical/nanotechnological systems. Therefore, no statistical analysis was performed.

RESULTS

The PubMed search yielded 1984 items. Among the collected studies, 1794 were discarded because they met the exclusion criteria. Full texts of 190 articles were retrieved and were further investigated. A total of 78 original studies were included in our review. The selection of the studies was performed according to PRISMA guidelines and the

process is presented as a flow diagram (Fig. 10) (59). More analytical, articles excluded are: reviews (358), case reports (173), clinical studies (93), clinical trial (71), Clinical Trial Protocol (3), Clinical Trial Phase I (3), Clinical Trial Phase II (2), Clinical Trial Phase III (2), Controlled Clinical Trial (52), meta-analysis (32), multicenter studies (34) observational studies (19), randomized controlled trial (50), research support N.I.H. Extramural (131), research support, N.I.H. Intramural (4), Systematic Reviews (41), research support US Government (167), research support US Government PHS (167), research support US Government Non-PHS (32), research support Non-US Government (453) and other types of articles (97). Eight (8) citations (60-67) were added after reviewing the bibliographies of the included papers. A full list of the articles included in the systematic review is presented in Appendix. The number of studies included, and their respective nano-field are summarised in Fig. 11. An overview of the type of the articles included and excluded, and the neurosurgical fields in which nanomedicine has been applied are reported in Fig. 12–14. We found eight studies pertaining to neuroimaging, ten studies dealt with neuro-nanotechnology, four had to do with neuro-regeneration, thirteen were about theranostics, and finally the majority of studies (a total of 43) were about neuro-nanotherapy. The distribution of the studies in fields of neurosurgery were: one in functional neurosurgery, one in head trauma, twelve in neurodegenerative diseases, forty-seven in neuro-oncology, nine in spinal surgery and peripheral nerves, six in vascular neurosurgery and two studies could apply to more than one fields (neuro-oncology and neurodegenerative diseases). The distribution of the studies through time is presented in Fig 15. Only four studies were conducted with human subjects (63, 66, 68, 69) and the rest were in vitro and in vivo studies on animals.

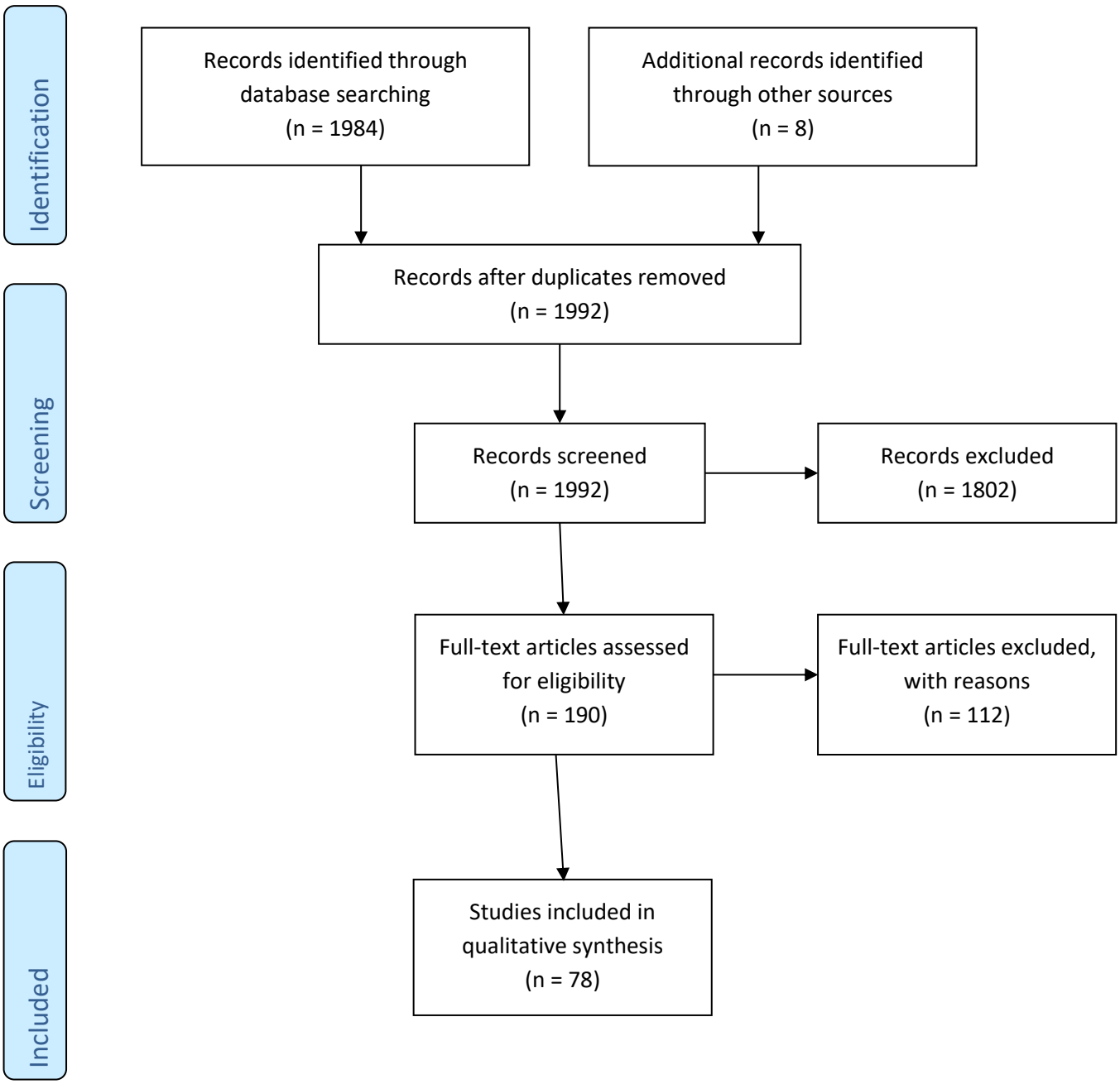

Figure 10. Flow diagram of selection according to PRISMA guidelines.

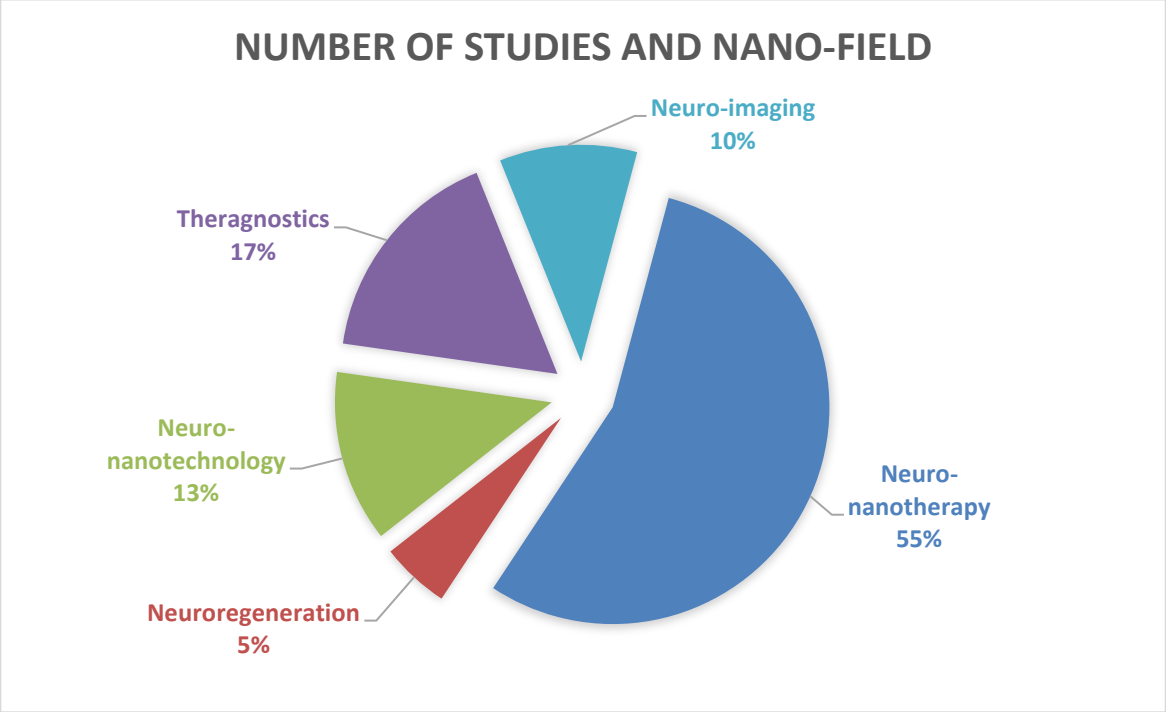

Figure 11. Analysis on Number of Studies according to Nano-field

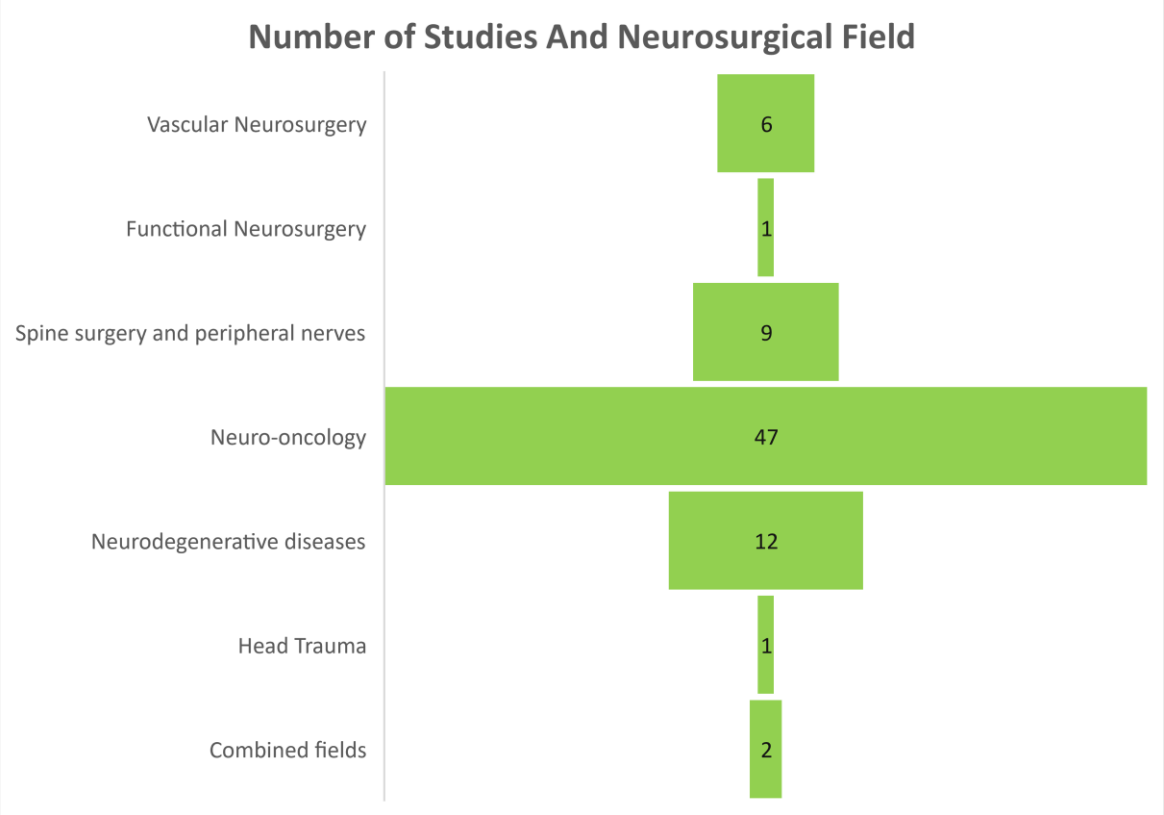

Figure 12. Analysis on Number of Studies according to Neurosurgical field.

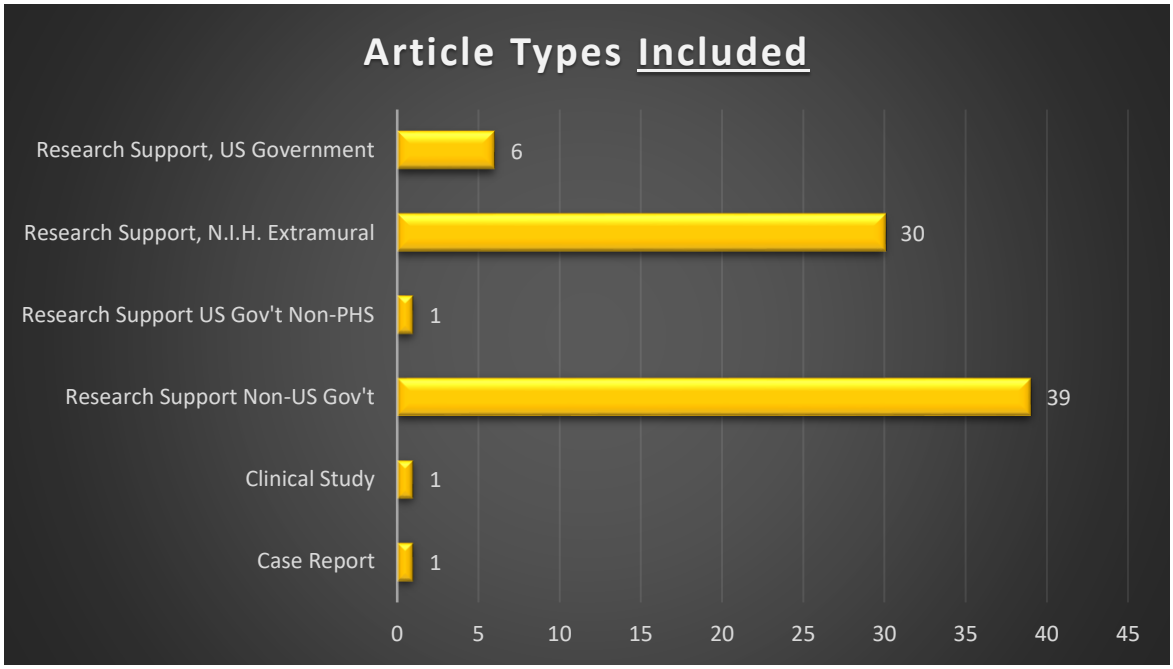

Figure 13. Number and type of articles included.

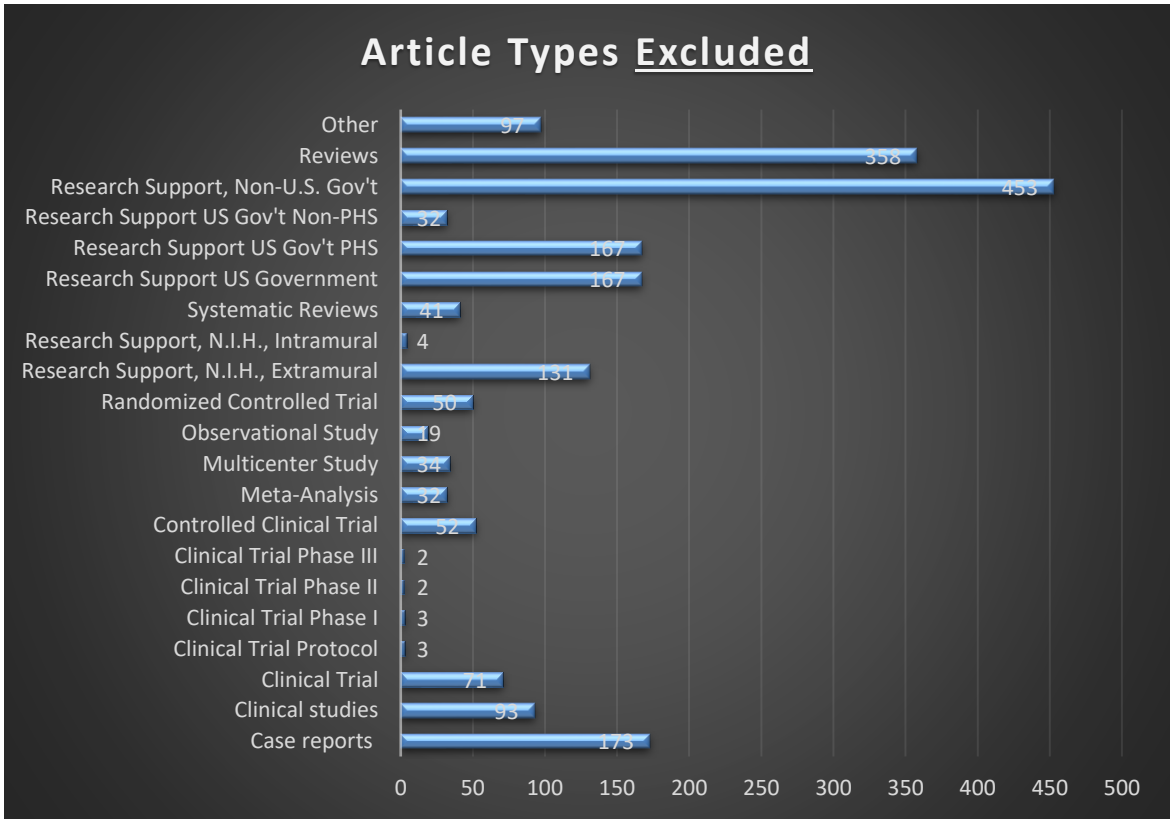

Figure 14. Number and type of articles excluded.

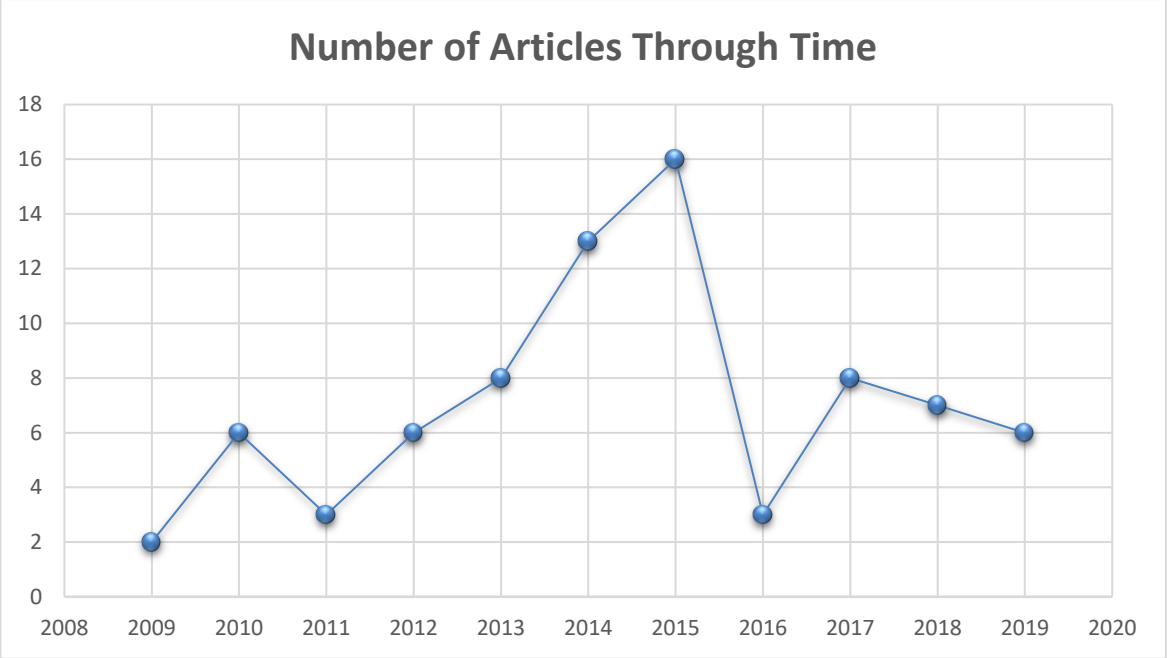

Figure 15. Distribution of articles through time.

Traumatic Brain Injury (Head Trauma)

Traumatic brain injury (TBI) is considered to be a clinical entity that represents a critical health problem worldwide. Even though, medical and surgical management of TBI have marked significant advances through the last ten years, it is still a health issue that affects nearly 10 million people annually (70). According to recent data, it is estimated that approximately sixty-nine million (95% CI 64-74 million) people worldwide suffer from a TBI yearly. Further analysis by continents showed that TBIs resulting from road traffic accidents were about 56% such as Africa and Southeast Asia and approximately 25% in North America. The incidence of traffic accidents for Southeast Asia and Europe was 1.5% and 1.2% of the population per year respectively. The overall incidence of TBI in North America, Europe, Eastern Mediterranean, Africa was 1299 cases, 1012 cases, 897 cases, 801 cases per 100,000 people (71). TBI is categorised as mild, moderate and severe. Mild TBI is also referred to as a brain concussion, which usually results from closed brain injury. Even though, it is considered to be a benign event, due to its potential neuropsychological effects in individuals who sustain more than usual brain injuries, such as military personnel, martial arts athletes, or professional football athletes, mild TBI drew much attention. TBI's pathophysiology is not yet fully elucidated. Its clinical manifestations come from the subsequent damage to neuronal axon during the injury. The neuronal axon can be stretched, sheared or intersected, which will eventually lead to axonal swelling, increased

cytoplasmic permeability, consecutively to calcium influx and finally to neuronal death (72).

In recent years nanotechnology and nanomedicine introduced newer technological advances and methodologies contributing to the early diagnosis of a mild TBI. Their main target is the identification of biomarkers at a micro- or nanomolecular scale either in blood or in cerebrospinal fluid (CSF) that reflects the loss of neuronal integrity, altered brain protein metabolism and altered synaptogenesis (73). Strongly predictive biomarkers of functional outcome in a mild TBI patient are considered to be myelin basic protein (MBP) and myelin-associated glycoprotein (MAG). These proteins are known products of both acute and chronic oligodendrocyte demyelination and are currently the subject of extensive research (74). The most recent nanotechnological advance is about a micro-chip with which brain-derived extracellular vesicles are nanomagnetically isolated. Using RNA sequencing and machine learning processing, the micro-chip can detect the extracellular vesicle micro-RNA (miRNA) cargo, which is correlated to the state of TBI. The study about this micro-chip claimed accuracy of 99% in identifying the signature of injured versus control mice, where the injured group consisted of a heterogeneous population. Furthermore, in the same study the intensity of the injury as well as the elapsed time since injury and the presence of a history of brain injury were also successfully predicted (75).

Functional Neurosurgery and Neurodegenerative diseases

In spite of intensive research, there is no effective treatment for neurodegenerative diseases. Current therapies focus only on treating the symptoms but do not stop the progression of the disease itself. Therefore, a slow progression of the disease drives the patient towards a debilitated state. Finding a treatment that can affect the course of the disease will likely have a much more significant impact on survival and quality of life. Nanomedicine and nanotechnology could potentially offer a solution to the treatment of Parkinson's disease (PD), Alzheimer's disease (AD) or Huntington's disease (HD). Because of the limitations of the CNS, it is very difficult to ensure long-term administration in the brain, yet nanotechnology has offered new formulations and has evolved as a new treatment for brain diseases.

Alzheimer's Disease

The most common cause of dementia in the modern world is AD, which is affecting approximately 40-50 million people worldwide (76) aged over 50 years. The first symptom of the disease is a symptom of mild brain dysfunction such as progressive episodic memory loss, that worsens slowly over the years. The cardinal pathological feature of AD is the formulation of amyloid plaques due to the aggregation of the amyloid-b (Ab) peptide. Consequently, intraneuronal neurofibrillary tangles develop in specific regions, and are composed of hyperphosphorylated forms of the microtubule-associated protein, tau (77). Furthermore, the brain is presented with significant neuronal loss and neuroinflammation (78, 79).

Current symptomatic treatment strategy includes cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and an NMDA receptor antagonist, memantine, for mild to moderate and moderate to severe AD respectively (80). New criteria of incorporate biomarkers have been established in order to identify AD at its early stages, and subsequently fight the progression of the disease by applying a strategy with disease-modifying drugs (e.g. lithium, rosiglitazone, tarenflurbil), psychotropic agents and psychosocial interventions (81, 82).

Nanomedicine has offered a lot in the treatment of AD. Newer drugs have been developed, and old ones have been improved with the help of nanocarriers, increasing the bioavailability of the drug and enhancing the levels of the active pharmaceutical agent (83, 84). Furthermore, nanomedicine has been targeting Aβ amyloid, by deploying strategies that can affect either the formulation of the amyloid or its breakdown (85, 86). Modern treatment strategies include promising and quite popular gene therapy (87, 88) and combined modalities. The latter refers to the use of ultrasound or MRI in order to temporarily open the BBB and either increase the bioavailability in the brain of the nanodrug or the conventional drug or promote a drug which could not formerly pass the BBB (89, 90). Finally, nanotechnological advances, such as biosensors with nanosheets, have also been very promising in diagnosing AD in its early stages (64).

Parkinson's disease

Parkinson's disease (PD) is the second most common chronic, progressive neurodegenerative disorder, after Alzheimer's disease. The prevalence of the disorder is generally accepted to be 1-2 per 1000 in the general population, whereas in people over the age of 60 years is 1% (91). PD is rare below the age of 50 years, whilst the prevalence in high age groups can reach up to 4%. The annual incidence per 100,000 people is approximately 5-20 (92). The clinical manifestations of PD include the classic triad of resting tremor, bradykinesia, and muscle rigidity, while also common symptoms are impaired postural reflexes, and varying degrees of autonomic dysfunction. The most distinct pathologic characteristic is the degeneration of dopaminergic neurons which lie in the substantia nigra pars compacta and the presence of intracytoplasmic inclusions (a.k.a. Lewy bodies) in these neurons (93). Many neurotransmitters are involved in direct, indirect and hyperdirect pathways in the basal ganglia circuitry, which translates to the use of several drugs daily in order to improve different aspects of the PD symptomatology such as motor, emotional, and cognitive symptoms, or psychiatric complications (94). The most prominent medication in the treatment of PD is levodopa, but other medications such as monoamine oxidase type B inhibitors (MAOBIs), amantadine, anticholinergics, b-blockers, and dopamine agonists can be an option in order to avoid levodopa-related complications (95). Most of the long-term side effects of levodopa are related to its brief activity, which corresponds to a pulsatile kind of stimulation of dopamine receptors, instead of continuous stimulation, which is present in the normal nigrostriatal pathway (94). Even though there are many drug delivery systems, including infusion pumps and skin patches, in order to provide a more continuous stimulation resembling the normal physiology of dopamine receptors, the desired effect has not yet been established (96, 97).

Nanomedicine has offered in PD treatment strategy newer drug delivery systems that can increase the bioavailability of existing drugs (83) but can also be used in the delivery of newer treatments such as gene therapy (84). Furthermore, most popular are the combined therapies as described above in AD, which includes an ultrasound or MR stimulus in order to temporarily disrupt BBB and allow the passing of several drugs (87-90). Nanotechnology has also offered very promising results in detecting PD with the help of biosensors based on gold nanoparticles, quantum dots or carbon nanotubes (98-100).

Besides pharmacological advances in the treatment of PD, nanotechnology has developed newer carbon monofilament electrodes that can produce even better results in electrophysiology study during deep brain stimulation (101).

Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, caused by an abnormal expansion CAG within the Huntingtin (HTT) gene. Most common pathologic signs of the disease are the extensive neuronal degeneration in the neocortex and the neostriatum, which leads to the main clinical manifestations of the disorder i.e. bradykinesia, cognitive decline, psychiatric disorders and the hallmark, progressive involuntary choreatic movements (102).

Nanomedicine has offered in HD treatment strategy mainly by devising better nano-delivery systems for gene therapy (83, 84). Promising results also yielded by combining treatment strategies, i.e. focused ultrasound, in order to enhance vascular permeability and open BBB for delivering liposomes carrying plasmids for gene therapy of HD (103). Moreover, nanomedical advances also contribute to the construction of better research mechanistic models in order to investigate the molecular pathophysiology of neurodegenerative movement disorders such as HD, giving as well insights of their clinical manifestations (65).

Neuro-oncology

Tumors of the CNS are considered one of the most significant challenges in neurosurgery not only due to their morbidity and mortality rate but also due to the surgical skill, which is needed in order to offer the patient a good post-operative quality of life. Recent research has turned to nanotechnology and nanomedicine for modern therapeutics and innovative nanobiological and nanotechnological platforms. Therefore, any nanoparticle that can be developed, such as liposomes, polymeric nanoparticles, dendrimers, quantum dots, supermagnetic nanoparticles, carbon nanomaterials, gene therapy and immunotherapy delivered by nanosystems, has been tested against a brain tumor. Many existing anticancerous medication have been enhanced by nanotechnology, in a way that diminishes the adverse effects of the active drug and improves both the bioavailability and the efficacy. In a phase 1 trial to assess safety and pharmacokinetics, 34

patients received intravenous administration of liposomal irinotecan and did not show any signs of toxicity (69). Nanodiamonds have been used to enhance the effect of doxorubicin. The nanosystem of doxorubicin has been studied in a preclinical glioma model administrated with the convection enhanced delivery method, and demonstrated quite promising efficacy (104). Doxorubicin has also been conjugated with polyethylene glycol (PEG) and a biodegradable, non-toxic, non-immunogenic platform, PMLA [poly(b-l-malic acid)]. This nanosystem has successfully demonstrated its efficacy in in vitro glioma cell lines but even in several breast carcinoma cell lines (105). Liposomes and polymeric nanoparticles have served well drug delivery in neuro-oncology offering new perspectives and providing with promising results with a variety of chemotherapeutic agents such cisplatin, oxaliplatin, paclitaxel and temozolomide (106-112). However, nanodrug delivery systems have also been used for delivering gene therapy. Polymeric nanoparticles showed good efficacy in transporting non-viral gene therapy (113-115), whilst intranasal administration of plasmid DNA nanoparticles resulted in long term gene changes in the rat brain (84).

Nanotechnology has also been deep in neuro-immunology using the immune system and its components (116, 117) in order either to deliver inhibitors (118) or to apply immunotherapeutic treatments (119, 120). Encapsulated lipid-nanoparticles aim at untargeted tumor RNA in an effort to activate an immune response in favor of the patient (121), whilst liposomes with GGTase I (geranylgeranyltransferase I) demonstrated inhibition of diacylglycerol kinase alpha for the treatment of resistant mesenchymal glioblastoma brain cancer phenotype (122). Other nanomedical advances include the use of dendrimers as a carrier system for epidermal growth factor. Their intratumoral or intracerebral administration showed enhanced efficacy in comparison to the administration of non-nanoconjugated epidermal growth factor (123). Another promising nanocarrier system is magnetic nanoparticles. Iron oxide nanoparticles conjugated to monoclonal antibodies demonstrated not only an antitumor effect (124) but can also enhance radiosensitivity of the glioblastoma (125).

Quantum dots and gold nanoparticles are particularly preferable in the research for brain cancer treatment. The main reason for this is their ability to be used as both neuro-imaging and neuro-therapeutic mean. This gave birth to a new concept that of

theranostics. The idea of simultaneously imaging and treating the tumor is gaining much more attention in the last decade. Semiconductor quantum dots have been used to label and modulate microglia and at the same type act as a carrier system for a tumoricidal drug (126). The synthesis of near-infrared quantum dots presents with good physico-chemical characteristics that are used both to depict gliomas and to apply photodynamic therapy (127). Furthermore, quantum dots have modified in that way to be able not only to easily cross the BBB but to fluorescence as well glioma and its tumoral vasculature (128). Carbon nanodots with high water solubility have also been modified in order to enter glioma cells and fluorescence in vivo gliomas (129). Oxide nanoparticles have been also optimised to therapeutically target specifically gliomas and it was demonstrated that could increase cellular uptake of the carried drug in in vitro studies (130) but also increase animal survival in several studies (131, 132). Iron particles have also been used in combined treatment strategies for gliomas. More specifically, magnetic iron nanoparticles have been injected in tumor-bearing rats and afterwards an exogenous magnetic field has been applied in order to cause hyperthermia of the tumor (133). Superparamagnetic iron oxide nanoparticles have been used as a delivery system for immunogenic peptides and stimulants of the neural system contributing in this way to the immune system's response to cancer (134). Finally, ultra-small gadolinium oxide nanoparticles have been shown to have great potential in the visualisation of glioma cells (135).

Gold nanoparticles are the spearhead of nanotechnology because they offer a great variety of applications and they have been extensively used in the treatment of gliomas. Gold nanorods have been delivered inside the tumor with neural stem-cell mediated delivery and combined with photothermal therapy they have decreased the recurrence rates not only for gliomas but even for breast cancer as well (136). Gold nanoparticles have also been conjugated to know chemotherapeutic agents such cisplatin. The administration of this nanosystem has been combined to an MR-guided focused ultrasound to intensify glioblastoma treatment, which achieved great results in the growth reduction of GBM tumors (137). Moreover, gold nanoparticles have been combined with immunotherapy. Gold-nanoshell loaded macrophages have been used in hyperthermia treatment applications and they demonstrated the potential of monocytes to be used as nanoparticle vectors for light-based cancer therapies (138). BBB disrupting based therapies are another

nanotechnological idea that uses magnetic fields and/or ultrasound to temporarily disrupt BBB and thus allow the passage of a nanodrug (139-141). Despite the rapid development of theranostics, neuro-imaging has also been evolved and offer promising results in depicting the brain tumor. This can help in diagnosis, follow-up but even in the surgical excision of the tumor. In this category, 5-aminolevulenic acid is used perioperatively to fluorescence the tumor and to improve the resection of the tumor (142). A nanotechnological advance, the hand-held Raman scanner, could accurately detect gold-silica surface-enhanced Raman scattering nanoparticles that are embedded in glioblastoma and thus guide a complete resection (143). Other nanotechnological advances include nano-scaffolds and magnetic carriers, such as magnetic liposomes, that can demonstrate high specificity and efficacy in tumor growth (144-146). Transferrin modified nanoscaled graphene oxide doxorubicin exhibited a significantly improved effect on tumor growth (147), as well did a thermosensitive liposome which demonstrated even better results than the conventional liposomes (148). Last but not least, liposomes have also been used in the treatment of tumor-like pathologies of the brain, such as abscess, reducing the toxicity of an intraventricular or intrathecal delivery and enhancing the effect of the active drug (68).

Spine surgery and Peripheral nerves

Spine surgery and peripheral nerves are a field of continuous and very promising research not only in medications but technological advancements as well. Newer applications in spinal fusion, drug delivery, neuronal and disk regeneration, prophylaxis for spinal infection, and molecular imaging are just a sample of areas that modern bioengineering and medicine can offer to neurosurgery. Nanotechnology has offered a lot in spinal fusion by engineering new materials with extraordinary physico-chemical properties. Nano-roughened surface modifications of existing titanium interbody implants have been reported to promote the differentiation of stem cells into osteoblast lineage with better results than the widely used and well-established polyetheretherketone (PEEK) cages (63, 149). Furthermore, newer bioabsorbable, self-retaining fusion cage has been developed and can offer better results in terms of stability and fusion in comparison again with PEEK (62). In addition to cages, gel scaffolds of bone morphogenetic protein-2 (BMP-2) binding peptide amphiphile nanofibers reported to promote osteogenesis and therefore

achieved both endogenous and exogenous fusion (61). Another area of spine surgery, spine trauma, received a lot of attention and research. Nanotechnology has developed better materials that can be used for filling fractured vertebrae instead of traditional cement. Electrospun nanofibrous poly(D, L-lactide-co-e-caprolactone) balloons have been manufactured and tested for filling a compressed fractured vertebra, and present with the advantages of calcium phosphate cement but without disadvantages (60). Regenerative medicine is a promising multidisciplinary field of research that encompasses translational research, tissue engineering and molecular biology. Nanotechnology has found a place in that field and offer very promising therapies to spine surgery and peripheral nerves. Composite hydrogels of drug-loaded poly lactide-co-glycolide (PLGA) nanoparticles are being investigated for their potential intrathecal administration in spinal cord injuries (67). Nanotechnology has also developed scaffolds and nanofiber nets that are used to promote functional recovery and nerve regeneration. For example, linear-ordered collagen scaffold fibers with collagen-binding brain-derived neurotrophic factor have been implanted in a complete transection of the spinal cord in canine and demonstrated a quite promising therapeutic effect in spinal cord injury. Nanofibrous membranes produced by the electrospinning process were used to assess the cicatrization process and prevent excessive scar formation, with good results (150).

Moreover, nanotechnology offered promising results in nerve regeneration, bridging the neural gap over 2 cm, which is approximately the threshold for neurorrhaphy. Thus, highly aligned nanocomposite scaffolds produced by electrospinning and electrospraying have demonstrated great potential in promoting and guiding regeneration and tissue growth of neurites (151). Other approaches in neural regeneration include an immunomodulatory approach. A CX3CR1 ligand has been used to stimulate nerve repair in a nerve-guidance scaffold. The study suggested that the infiltrating immune cellular milieu after nerve injury propagates regeneration and creates a favorable environment for repair (152).

Vascular neurosurgery

Neurovascular disorders can be dealt either by conventional neurosurgical approaches or by endovascular techniques, or a combination of them. The three main

categories that vascular neurosurgery must deal with are aneurysms, vascular malformations and stroke. Aneurysms are an abnormal dilatation of the artery that can take several shapes and present with a high risk of rupturing. They are characterised by internal elastic lamina and media disorder, which result in a focal weakness and therefore the formation of the aneurysm. The frequency of aneurysms occurring in the general population is variable and ranges from 2% to 5% (153). They are classified according to their size, shape and their pathogenesis. Thus, according to size there are small aneurysms that have a diameter of less than 1.5 cm, large aneurysms with a diameter of 1.5 – 2.5 cm, and giant aneurysms over 2.5 cm of diameter. According to their shape, they are classified as saccular, fusiform and microaneurysms. Finally, they are classified according to their etiology and they can be of infectious etiology, traumatic or even associated with tumors (154-156). Vascular malformations are comprised of cavernomas (CM), arteriovenous malformations (AVMs), developmental venous anomalies (DVAs), and capillary telangiectasias (CT). Their clinical manifestation is more frequent in the middle decades of life and it is usually either seizures or haemorrhages. CM is found in 0.16-0.5% of the general population and its etiology has not yet been elucidated (157, 158), although in 10% of patients with CM three genes have been identified (159, 160). Arteriovenous malformations are congenital lesions, that usually appear in the 3rd week of gestation. They are a tangled network of arteries and veins of various sizes which they communicate without a capillary system. Therefore, the nidus, which is the hallmark of AVMs, is formed in the core of that network. Asymptomatic AVMs are found in the general population at a rate of less than 1%. Developmental venous anomalies, which are also known as venous angioma, present with a prevalence of 6.4% (161), and they are usually an accidental finding. Brain capillary telangiectasias (CTs) are rare entities with a very low prevalence of 0.4% (162, 163). They are characterised by a benign clinical course, although their presence has been correlated with several clinical syndromes such as Osler-Weber-Rendu syndrome or Sturge-Weber (164). Finally, stroke is classified into two categories the ischemic stroke and the hemorrhagic. Ischemic stroke is the fifth leading cause of mortality and morbidity in the modern world (165, 166). Ischemic strokes account for approximately 87% of all stroke and nearly 1 out of 4 people have had a history of a previous stroke (167). The hemorrhagic stroke represents 10-15% of all stroke, and it is linked with a higher mortality risk than the ischemic (168, 169). Nowadays with the increasing use of anticoagulants, the

incidence of hemorrhagic stroke keeps rising. Main risk factors comprise of hypertension, cerebral amyloid angiopathy or anticoagulation.

Advances in research in the last ten years include imaging and identification of vascular disorders and newer therapeutic agents that are focused in neuroprotection. Many nano-systems based on liposomes have incorporated a variety of molecules such as melanin, VEGF with transferrin, and even hemoglobin in order to provide a neuroprotective effect on the ischemic brain. Their effect is possible through scavenging of excessive reactive oxygen and nitrogen species (RONS) but promoting as well vascular regeneration and microvascular perfusion (170-172). Pertaining to therapy strategies nanomedicine has developed new masking techniques from the human body immune system offering thus existing drugs such as tPA, with greater bioavailability, less systemic adverse effects and better targeting (173). In terms of neuroimaging, nanomedicine has helped a lot with the introduction of quantum dots and nanoparticles such as ultra-small superparamagnetic iron oxide nanoparticles. These agents can be used as a macrophage imaging agents resulting in the visualisation of inflammatory cells and thus identifying endothelial damage for early detection of aneurysms or any other intracranial vascular malformation with a high probability of rupture (66). These achievements could help in the future even in identifying vascular distributions predisposed to vasospasm or in distinguishing penumbra from the infarcted area.

Neurosurgical Field	Nanomaterial
Vascular Neurosurgery	• Liposomes • Polymers • USPIONs • Melanin NPs
Functional Neurosurgery	• Carbon monofilament electrodes
Spine surgery and peripheral nerves	• Nanospheres (e.g. Polymersomes core-shell) • Nanoscaffolds • Nanopolymers • Hydrogels • Nanofibers
Neuro-oncology	• Liposomes • Nanopolymers • Nanodiamonds • mRNA-NPs • IONPs and SPIONs • Dendrimers • Quantum dots • Gold NPs, nanorods, nanoshells • Hydrogels • Magnetic NPs • Graphene oxide • Nanoscaffolds • Nanocrystals
Neurodegenerative diseases	• Magnetic NPs • Gold NPs • Liposomes • Nanofibers • Nanopolymers • Single-wall carbon nanotubes • Graphene quantum dots • Nanosheets
Head Trauma	• Lab on chip

Table 3. Summary of nanomaterials for each neurosurgical field.

LIMITATIONS OF NANOTECHNOLOGY AND NANOMEDICINE

Even though nanotechnology and nanomedicine have tremendous potential in diagnosis, therapy and theranostics, there are still under investigation and their implementation in surgical practice is still young. Current research has focused on the toxicity of nanoparticles, since there is uncertainty over long-term effects of NPs in the CNS. The small size of NPs translates to a larger surface area being exposed to the body per unit mass, in comparison to conventional agents, and thus increased reactivity (174, 175). Nanomaterials that are based on graphene have been proved to be cytotoxic because they are responsible for the generation of excessive reactive oxygen species that overcome cell's antioxidant mechanisms (176). Furthermore, graphene can cause DNA fragmentation and chromosomal aberrations (177). Another problem of NPs is their retention within the target organ, e.g. the brain. Even though surface functionalization is a useful technique to improve tissue targeting, it will eventually increase the size and decrease their clearance from the kidneys. Subsequently, a dilemma is born. This conundrum was dealt partially by the development of biodegradable nanomaterials. Nevertheless, these materials present with a variety of degradation rate, they come in different batches of the same nanomaterial (178), they accumulate after repeated administration and consecutively the problem remains. Furthermore, patients with hepatic or renal insufficiency can also present a reduced clearance of the NPs, which leads to an accumulation beyond the therapeutic target range (179).

Even though nanodrugs are considered to be the spearhead of technology and with great potential, their efficiency has been challenged a lot. A meta-analysis which included 14 clinical trials on pegylated liposomal antibiotics demonstrated that the therapeutic outcome in humans is not as good as in animal studies (180). In spite of the fact that liposomes are the most commonly used particles in nanodrugs and have a good pharmacological basis, they have not performed as expected in phase 3 clinical trials. An explanation given is that their efficacy is decreased because of strong interactions with the patient's immune system. For example, it has been reported that in cancer patients, high or low peripheral blood monocyte count was linked to increased or decreased clearance of pegylated liposomal doxorubicin respectively (181-183). Other studies have demonstrated that combination models of pegylated liposomal doxorubicin and

checkpoint inhibitors of the immune system have enhanced anticancer activity in immunocompetent mice (184-187). Therefore, the interaction of nanodrugs with the innate immune system of the patient must be a target of further investigation.

DISCUSSION

The use of nanotechnology in medicine is set to spread rapidly, and there is increasing optimism that it will bring important advances in both the diagnosis and the treatment of a disease. Most promising applications include the fields of drug delivery, in vitro as well as in vivo diagnostics, nutraceuticals and production of improved biocompatible materials. The nano-biotechnology research is mostly oriented in developing more specific drug targeting and delivery systems, in reducing toxicity but maintain the same therapeutic effect, and in the faster development of safer and bio-compatible medicines. The main applications of nanoparticle technology are in cancer therapy, in diagnostic testing, in HIV and AIDS treatment and brain pathology.

Conventional cancer treatment today has been the gold standard in the fight against cancer. Nevertheless, most of the times, the side effects of treatment are debilitating and subsequently constitute the main cause of poor patient compliance. Conventional cancer treatment lack specificity resulting in side effects affecting the entire body. Current chemotherapeutic agents are aiming all rapidly dividing cells, which is the hallmark of cancer cells. However, there are healthy cells such as hair follicles and intestinal epithelium that are also affected by chemotherapy and leave the patient dealing with life-changing adverse effects (188). Nanotechnology has provided specially designed nanoparticles that can pinpoint and act against specific target cells inside the body avoiding adverse effects from other healthy organs (189, 190).

Micelles and liposomes are at the line of fire and offer a highly specialised drug carrier to cancer cells. Due to their duality (hydrophobic core and hydrophilic shell) they can offer solubility to an insoluble drug. Moreover, micelles can become stealth when they are coated with PEG. Consequently, if a micelle's surface is PEGylated, then the new nanocarrier can pass through fenestrated vasculature tumors as well as through inflamed tissues via passive transport. Liposome nanocarrier systems are being investigated for their ability to be organised to multi-carrier systems for both chemotherapeutic agents (e.g.

doxorubicin) and cancer antibodies (191). These systems contribute to theranostics. To this day, several nanocarrier systems such as paclitaxel-loaded polymeric micelle (Genexol-PM), pegylated doxorubicin (Doxil/Caelyx), liposome-encapsulated doxorubicin (Myocet) against breast cancer, liposome-encapsulated daunorubicin (DaunoXome) against HIV-related Kaposi sarcoma and the more recently nanodrug Nab-paclitaxel in combination with gemcitabine (Abraxane) against metastatic pancreatic cancer have been approved by the FDA and the EMA (192, 193). Dendrimers are highly branched multi-potent macromolecules that can offer in targeting, imaging and treatment (194, 195). The profile of each system is constituted by their ability of absorption, distribution, metabolism and elimination (196, 197). Such a system has been reported for the in vitro delivery, localisation and imaging of the anticancer agent methotrexate (198). Other forms of nanoparticles have also shown great potential in cancer treatment. Niosomes have been used as potential drug carriers in cancer research. Recent reports documented intravenous administration of niosomes targeting breast cancer transferrin receptors (199). Fullerene spherical molecules C60 and their derivatives (200) can act as a scavenger of reactive oxygen species (ROS), while its nanocrystals can enhance the effect of chemotherapy (e.g. when combined to doxorubicin) (201-203).

Diagnostic testing is being hindered by inadequacies of fluorescent markers, for which the use of nanoparticles in diagnosis is currently being explored and provide new solutions overcoming those problems (204). The most important discovery was that of quantum dots. Their ability to absorb light from ultra-violet to within visible spectrum and tune their emission place them as a very promising imaging agent (205, 206). However, the main advantage is that they can be combined with several biomolecules that can remain in a living system a considerable amount of time. This ability allows scientists to monitor the desired biological effect by simultaneously tagging various molecules of biological pathways (207).

Nanotechnology has been most helpful in the fight of the human immunodeficiency virus (HIV). It has been most effective in delivering antiretroviral drugs and in improving patient compliance. There are various articles that report successful targeting of nanoparticles conjugated with antiretroviral drugs to macrophages and monocytes in in vitro experiments (208, 209). Exploiting the superiority of nanoparticle

systems in embedding several antiretroviral agents, investigators have proven sustained drug release for several weeks, even in difficult to access areas such as the brain (210-212).

The brain is probably the most challenging target organ for drug delivery. The main challenge is to overcome the natural barrier of the blood-brain barrier (BBB) (213). Coating nanoparticles with polysorbate surfactants was a popular strategy to get through BBB (214). The mechanism proposed was endocytosis via low-density lipoprotein (LDL) receptors of the endothelial cells. Other routes bypassing BBB are olfactory or trigeminal migration (215), where translocation of particles has been detected using isotope measurements. In order to augment the uptake through inhalation routes nanoparticles have been conjugated with bioactive ligands-lectins to the surface of poly (ethylene glycol)- poly (lactic acid) (PEG-PLA) nanoparticles. This technique has increased by two-fold brain uptake of inhaled nanoparticles (216).

Nanotechnology has great potential in helping neurosurgery. The majority of nanomedical advances are about brain tumors. New drug delivery nanosystems have been developed in order to bypass the brain-tumor barrier and offer greater bioavailability of chemotherapeutic agents. Doxorubicin, paclitaxel and temozolomide are widely used chemotherapeutic medicines and when combined with nano-drug delivery systems, they can be more effective with less side-effects (105, 106, 111). Furthermore, nanomedical advances offered new perspectives on gene therapy. Mangraviti et al showed that polymeric nanoparticles could be a good delivery system for non-viral gene therapy (113). Thus, the way for a personalized tumor treatment does not seem to be far away (121). Nevertheless, nanotechnology has helped not only in tumor therapy, but also in a better diagnosis of tumors. Magnetic nanoparticles and gold nanoparticles have been used to provide a better result in both depicting the tumor and for treating it at the same time (131, 133, 136). These are applications of a new field, called theragnostics. The same logic behind these applications are used to offer better treatments to neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease and Huntington’s disease. Liposomes, polymersomes and gold nanoparticles have been applied for the diagnosis and treatment of those diseases (85, 98, 103). Moreover, nanotechnology has been used to develop better scaffolds for neural regeneration, which have been tested in nerve gaps and even in spinal cord injuries and presented with promising results (150, 151, 217).

Newer nanomaterials have also been developed to offer better stabilization in spine surgeries (61, 63). In addition, materials that have been nanotechnologically manufactured, they have been a good solution for developing devices for diagnosing head injury or even improve neurophysiological diagnosis on deep brain stimulation surgeries (75, 101). Finally, nanomedical advances have been a promising alternative to vascular neurosurgery for ischemic strokes, arterial or venous malformations and aneurysms (66, 171, 173, 218).

FUTURE PERSPECTIVES AND NEEDS

An ideal nanoparticle drug delivery system should be able to reach, recognise, bind and deliver its load to pathologic tissues with high specificity and sensitivity, avoiding interaction with the immune system and minimise or avoid drug-induced damage to healthy tissues.

Even though there is an extensive amount of reviews on the toxicity of nanoparticles, this data refers to a small group of nanoparticles. Most of the research is oriented on obtaining a significant reduction of the drug carried in a nanosystem, but not on possible toxicity of the system. A recent report has identified four possible mechanisms of NP toxicity: a) toxicity of one of the constituents with the same mode of action as the bulk chemical, b) toxicity due to degradation products, c) due to endocytosis of the NPs, and d) membrane lysis due to the NPs possibly via chemical toxicity. For instance, some NPs, which get airborne may pose inhalation problems, cosmetics could pose dermatological problems, while NPs for parenteral use interactions with blood components, systemic distribution and kinetics are of great importance. Each nanosystem should be tested on a case by case basis focusing on their portal of entry. Therefore, a uniform classification by risk of a nanosystem and the anticipated application should be devised.

The epidemiological evidence on ultrafine particles has revealed several effects and mechanisms of action. However, whether these concepts can be extrapolated for all manufactured NPs is yet unknown. It must be taken into consideration that a growing set of materials, whose properties are yet to be discovered, are primarily used in the research. Therefore, a logical question is posed. Are our current regulation protocols robust enough

to test, classify and approve the effectiveness and the toxicity of each NP system? Subsequently, should the precautionary principle be used in nanotechnology? Pointing out that scientific uncertainty is no reason for inaction even though strong adverse effects are present, may be useful in developing nanotechnology where scientific information is still young. Nevertheless, the risks should be taken into consideration, and the applications of nanotechnology should be employed with care.

The ultimate target for nanotechnology is the brain. Incidence of brain pathology is rising as the population ages, and convectional medicaments prove to be insufficient for dealing with neurological diseases. Moreover, the brain bears the blood-brain barrier, the famous most selective gatekeeper of the body, which protects highly functioned cells with prolonged regeneration rate, neural cells. Nanotechnological research is still young for the neural system, yet quite promising and many new nanosystems are nowadays under severe scrutinise in clinical trials for brain pathology. However, neuroscience tends to be a distinct promising branch of research, where neuroscientists develop into a different kind of researcher. Consecutively, nanotechnology should spawn a new sector, neuro-nanoscience. This area should be strictly oriented in researching, knowing and understanding molecular mechanisms of neural systems and their interaction with nanotechnology.

Finally, even if all the aforementioned issues have been solved, there are yet two major problems to be dealt with. These refer to reproducibility and similarity. To this point, research has not been able to reproduce an exact copy of a nanosystem. Each batch of a nanodrug is slightly different from the previous one. Thus, one should think what makes a nanodrug same with its next formulation? Are its properties reproduced? Obviously, science should set the limitations to what a reproducible nanodrug is. Consequently, similarity should also be examined. If a generic drug cannot be produced and safely administered, will the original nanodrug be cost-effective? Therefore, reproducibility and similarity are essential features of a nanodrug and should be included in new regulations of nanotechnology, in order for a nanosystem not only to be effective but also cost-effective.

CONCLUSION

Drug delivery nanosystems have undoubtedly offered numerous solutions and alternatives to problems related to conventional methods performed by Medicine until today, such as cancer. The blooming of pharmaceutical nanotechnology, along with the development of related techniques, allowed the exploration of phenomena that are associated with the nanoscale and were not observed in the macrocosm. Nanomedicine is a rapidly growing field, but in the same way that scientists examine carefully every new scientific area, there are also plentiful questions arising, concerning the safety, toxicity, efficiency, ethics and possible dangers related to it. Additionally, hundreds of drug delivery nanosystems reach the point of clinical trials, but not all are yet commercially available. Their in vivo behavior needs to be reexamined and physiological barriers, conditions, cells' barriers need to be taken into consideration. Consequently, it is highly desired to discover new methods of producing more efficient nanosystems. Their toxicity needs to be evaluated and new legislation needs to be established, in order to protect humanity, the environment, personal data and to prevent in general a malicious use of nanotechnology. Nanomedicine is a precious tool with inconceivable properties and perspectives and as a result, society should control and direct its applications towards a better humanity.

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